NEOADJUVANT CHEMORADIATION IN LOCALLY ADVANCED RECTAL CANCER

A dissertation submitted to

the Tamilnadu Dr. M.G.R. Medical University, Chennai,

in partial fulfillment of the requirements for the award of

the degree of

DOCTOR OF MEDICINE (M.D.) IN RADIOTHERAPY

March 2010

CERTIFICATE

This is to certify that this dissertation titled, "**NEOADJUVANT CHEMORADIATION IN LOCALLY ADVANCED RECTAL CANCER"** is a bonafide record of the work done by Dr Saritha D, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of her postgraduate study for the degree of M.D. (Branch IX – Radiotherapy) from 2008-2010 under my direct guidance and supervision.

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ACKNOWLEDGEMENT

I would like to express my heartfelt gratitude to Dr. S. Krishnamurthi, Advisor, Cancer institute and Dr. V. Shanta, Executive Chairman, Cancer Institute for providing me all the necessary facilities for this study.

I am very grateful to Dr. A.Vasanthan, Chairman, Division of Radiation Oncology, Cancer Institute, who has helped and guided me at each step with invaluable suggestions.

I am ever grateful to Dr. G. Selvaluxmy, Professor, Division of Radiation Oncology, Cancer Institute, who has always given constructive criticism. She has helped and guided me in completing this study.

I am deeply indebted and grateful to Dr. D.V.L.N. Sastry, whose very presence has given me lot of inspiration.

I express my gratitude to Dr. Alexander John for all his support I also thank Dr Satish srinivasan,Dr P.Satish Dr Jumi.B and other faculty members for all their support

I wish to thank all my peers and juniors, medical physicists, radiotherapy technologists and tumor registry staff, without whose support this study would just have not been possible. I whole heartedly thank all the patients who participated in this study.

I dedicate this work to my parents,parents in law, my husband and daughter who provided me with immense moral support and encouragement.

Dr. Saritha D

CONTENTS

INTRODUCTION

INCIDENCE AND GEOGRAPHIC VARIATION

Colo-rectal cancer accounts for almost 10 % cancer mortality in the United States. In almost all countries age standardized incidence rates are less for women than in men. In the US alone colo-rectal cancer is the second most common cause of cancer mortality and ranks third in frequency of cancer sites in both men and women (1, 2, 3). Incidence and mortality rates are the greatest in developed western nations. Chinese immigrants in the US have been observed with higher colo-rectal cancer rates. This has been attributed to their increased meat consumption and decreased physical activity. There is now a decrease in colo-rectal cancer incidence and mortality possibly due to alterations in dietary and lifestyle factors and enhanced use of colonoscopy with polypectomy (4, 5, 6). The crude incidence of rectal cancer in the European Union is approximately one third of the total colorectal cancer incidence, i.e. 15–25/100,000 per year. The mortality is 4–10/100,000 per year with the lower figures valid for females and the higher for males. Hence environmental exposure in colo-rectal cancer is of great importance and due attention should be paid to dietary and lifestyle modification as a preventive measure (7). Peak incidence rates are noted in Europe, US, Australia and New Zealand (8). The lowest incidence rates are noted in India and South America.

Madras Metropolitan Tumour Registry (MMTR) data

Crude incidence rate per 100,000 population (2006)

AGE	MALE	FEMALE
20-24	2.1	0.6
25-29	1.2	-
30-35	1.9	1.0
36-39	1.0	1.5
40-44	4.3	1.4
45-49	4.0	6.1
50-54	10.1	2.9
55-59	10.6	5.3
60-64	15.4	9.6
65-69	11.5	12.7
70-74	15.7	12.9
75+	15.1	12.6

The crude incidence rates of rectal carcinoma as recorded in the Madras metropolitan Tumour Registry were 3.3/100,000 in males and 2.1/100,000 in females during the year 2006.

RACE AND ETHNICITY

An inherited APC gene mutation, 11307K, confers a higher risk of colo-rectal cancer within certain Ashkenazi jewish families (9), but not very apparent in other ethnic groups. Inherited mutations in the DNA mismatch repair genes may be more common among African Americans (10).

ETIOLOGY

Many factors contribute to the etiology of colo-rectal cancer. It is complex and involves interplay of environmental and genetic factors (4, 6).

Environmental factors (22,23,24)

Increased Incidence	*Decreased Incidence*
High-calorie diet	Antioxidant vitamin consumption
High red meat consumption	Consumption of fresh fruit and vegetables
Overcooked red meat consumption	Use of nonsteroidal antiinflammatory drugs
High saturated fat consumption	High-calcium diet
Excess alcohol consumption	
Cigarette smoking	
Sedentary lifestyle	
Obesity	

Note: Coffee or tea consumption has no effect on incidence.

Family History

Family history confers an increased lifetime risk of colo-rectal cancer. About 15% of all colo-rectal cancers occur in patients with a history of colo-rectal cancer in first degree relatives (11, 12, 13).

Genes

The functions of the major colon cancer genes have been reasonably well characterized over the past decade. Three proposed classes of colon cancer genes are tumour suppressor genes, oncogenes, and stability genes (15, 16). Tumour suppressor genes constitute the most important class of genes responsible for hereditary cancer syndromes and represent the class of genes responsible for both familial adenomatous polyposis (FAP) and juvenile polyposis, among others (17, 18, 19, 20). Germline mutations of oncogenes are not an important cause of inherited susceptibility to colorectal cancer, even though somatic mutations in oncogenes are ubiquitous in virtually all forms of gastrointestinal cancers. Stability genes, especially the mismatch repair genes responsible for Lynch syndrome (also called hereditary nonpolyposis colorectal cancer [HNPCC]), account for a substantial fraction of hereditary colorectal cancer, as noted below (21). MYH is another important example of a stability gene that confers risk of colorectal cancer on the basis of defective base excision repair.

Following table summarizes the genes that confer a substantial risk of colorectal cancer, with their corresponding absolute risks of colorectal cancer for mutation carriers in hereditary colorectal cancer syndromes (25, 26, 27, 28)

Gene	Syndrome	Hereditary Pattern	Predominant Cancer
Tumor suppressor genes			
APC	FAP	Dominant	Colon, intestine, etc.
AXIN2	Attenuated polyposis	Dominant	Colon
TP53 (*p53*)	Li-Fraumeni	Dominant	Multiple (including colon)
STK11	Peutz-Jeghers	Dominant	Multiple (including intestine)
PTEN	Cowden	Dominant	Multiple (including intestine)
BMPR1A	Juvenile polyposis	Dominant	Gastrointestinal
SMAD4 (*DPC4*)	Juvenile polyposis	Dominant	Gastrointestinal
Repair/Stability genes			
hMLH1, *hMSH2*, *hMSH6*, *PMS2*	Lynch	Dominant	Multiple (including colon, uterus, and others)
MYH (*MutYH*)	Attenuated polyposis	Recessive	Colon
BLM	Bloom	Recessive	Multiple (including colon)

Gene	Syndrome	Hereditary Pattern	Predominant Cancer
Oncogenes			
KIT	Familial GI stromal tumor		GI stromal tumors
PDGFRA	Familial GI stromal tumor		GI stromal tumors

Syndrome	Absolute Risk in Mutation Carriers
FAP	90% by age 45 years
Attenuated FAP	69% by age 80 years
Lynch	80% by age 75 years
MYH-associated neoplasia	Not established
Peutz-Jeghers	39% by age 70 years
Juvenile polyposis	17% to 68% by age 60 years

APC gene on chromosome 5q21 encodes a 2,843-amino acid protein that is important in cell adhesion and signal transduction; beta-catenin is its major downstream target. APC is a tumour suppressor gene, and the loss of APC is among the earliest events in the chromosomal instability (CIN) colorectal tumour pathway. The important role of APC in predisposition to colorectal tumours is supported by the association of APC germline mutations with FAP and attenuated FAP (AFAP). Both conditions can be diagnosed genetically by testing for germline mutations in the APC gene in DNA from peripheral blood leukocytes. Most FAP pedigrees have APC alterations that produce truncating mutations, primarily in the first half of the gene. AFAP is associated with truncating mutations primarily in the 5' and 3' ends of the gene and possibly missense mutations elsewhere.

Molecular Events Associated With Colon Carcinogenesis

The transition from normal epithelium to adenoma to carcinoma is associated with acquired molecular events [29]. This tumour progression model was deduced from comparison of genetic alterations seen in normal colon epithelium, adenomas of progressively larger size, and malignancies [30]. At least five to seven major deleterious molecular alterations may occur when a normal epithelial cell progresses in a clonal fashion to carcinoma. There are at least two major pathways by which these molecular events can lead to colorectal cancer. About 85% of colorectal cancers are due to events that result in chromosomal instability (CIN) and the remaining 15% are due to events that result in microsatellite instability (MSI or MIN, also known as replication error).

The spectrum of somatic mutations contributing to the pathogenesis of colorectal cancer is likely to be far more extensive than previously appreciated. A comprehensive study that sequenced more than 13,000 genes in a series of colorectal cancers found that tumours accumulate an average of approximately 90 mutant genes. Sixty-nine genes were highlighted as relevant to the pathogenesis of colorectal cancer, and individual colorectal cancers harboured an average of nine mutant genes per tumour. In addition, each tumour studied had a distinct mutational gene signature. Key changes in CIN cancers include widespread alterations in chromosome number (aneuploidy) and detectable losses at the molecular level of portions of chromosome 5q, chromosome 18q, and chromosome 17p; and mutation of the KRAS oncogene.

Genetic polymorphism

This may be of great importance. The changes in glutathion s-transferase, ethylene tetrahydrofolate reductase and N-acetyl transferases cause genetic polymorphism. Though genetic polymorphism may vary among different racial and ethnic groups, it may provide some clue regarding geographic variation of colo-rectal cancer [31, 32, 33].

ANATOMY

The colo-rectum consists of caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon and rectum [34].

The sigmoid colon evolves distally into the rectum and the peritoneal coverage recedes. The rectum measures 12 to 15 cm in length, extends from the recto-sigmoid junction to the pubo-rectalis ring. The upper third of the rectum is draped with peritoneum anteriorly and onto both sides [35]. In the middle third of the rectum the anterior surface is covered with peritoneum, which forms the posterior-border of the recto-uterine pouch or recto-vesical space. The lower third of the rectum is devoid of peritoneal covering and is in close proximity to adjacent structures including the bony pelvis. Distal rectal tumours have no serosal barrier to invasion of adjacent

structures.

The true surgical rectum begins at the ano-rectal ring just proximal to the dentate line. This represents the internal anal sphincteric muscle which is responsible for anal continence.

The middle valve of Houston is a landmark identified endoscopically (usually about 6 cm from the ano-rectal ring) and can be used to differentiate proximal tumours from more distal lesions. Fascia of Waldeyer separates rectum from prostrate and fascia of Denonvilliers is present on the posterior aspect along the last two sacral vertebrae.

Lymphatic drainage of the upper rectum follows the superior rectal vessels, and empty into the inferior mesenteric node and those of the middle and lower rectum along the middle rectal vessels and terminate in the internal iliac nodes. The lowest part of the rectum and upper part of the anal canal share a plexus that drains to lymphatics that accompany the inferior rectal and internal pudendal blood vessels and ultimately drain to internal iliac nodes [35].

Lymphatics of the rectum

Carcinomas of the lower rectum or those extending into the anal canal may occasionally metastasize to superficial inguinal nodes via connections to efferent lymphatics draining the lower anus. The blood supply for the rectum is by superior, middle and inferior rectal arteries.

STAGING

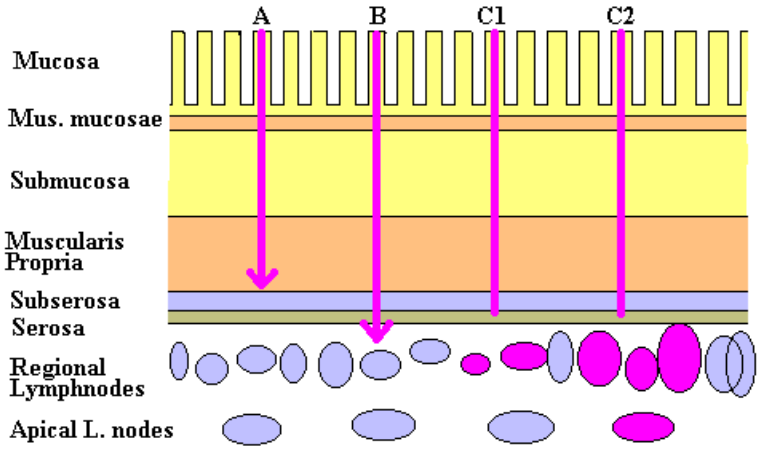
The staging of colorectal cancers is complicated by the fact that multiple staging systems are in use and there is no agreement on which staging system should be used. Although most staging systems rely on the depth of tumour invasion and absence or presence of nodal and distant metastases, there is no consensus on how various categories should be grouped. Since the description of the first practical staging system by Dukes, the evolution and modification of staging systems over last 60 years with newer systems

using similar notations to represent different stages has resulted in considerable confusion and misinterpretation. Apart from the Dukes' system [36] which is still widely used, the other popular systems include the classification described by Astler and Coller [37], and the tumour-node-metastasis (TNM) classification of the Union Internationale Contra le Cancer (UICC) [38] and the American Joint Committee on Cancer (AJCC) [39].

The Dukes' Staging System

The original Dukes' system was described for rectal carcinomas that can also be applied to carcinomas of the colon [40].

Dukes' Staging System



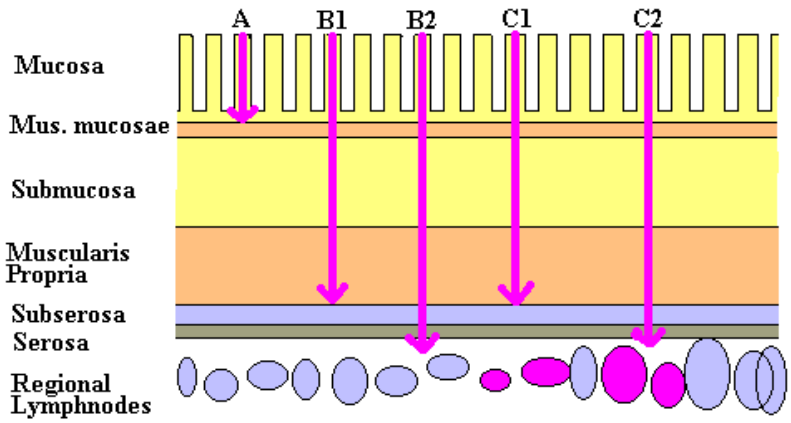
Stage A tumours were defined as those limited to the wall (not extending beyond muscularis propria), stage B as those extending through the wall (into subserosa and/or serosa, or extra-rectal tissues), and stage C as those

having lymph node metastasis. The stage C was later subdivided by Dukes himself into C1 when only perirectal nodes were positive and C2 when nodes at the point of mesenteric blood vessel ligature (called apical nodes) were involved. The stage D was added still later and was characterized by presence of tumour beyond the limits of surgical resection.

The Astler-Coller Staging System

This system [37] was proposed in 1954 and has resulted in some confusion because it is often misinterpreted as related to the Dukes' system.

Astler-Coller Staging System



The original scheme had five stages, A was limited to the mucosa, B1 involved muscularis propria but did not penetrate it, B2 penetrated the muscularis propria, and C1 and C2 were counterparts of B1 and B2 with nodal metastases. Since then, later modifications have added three more stages. B3 represents involvement of adjacent structures, C3 is B3 with nodal metastasis, and D signifies presence of distant metastasis.

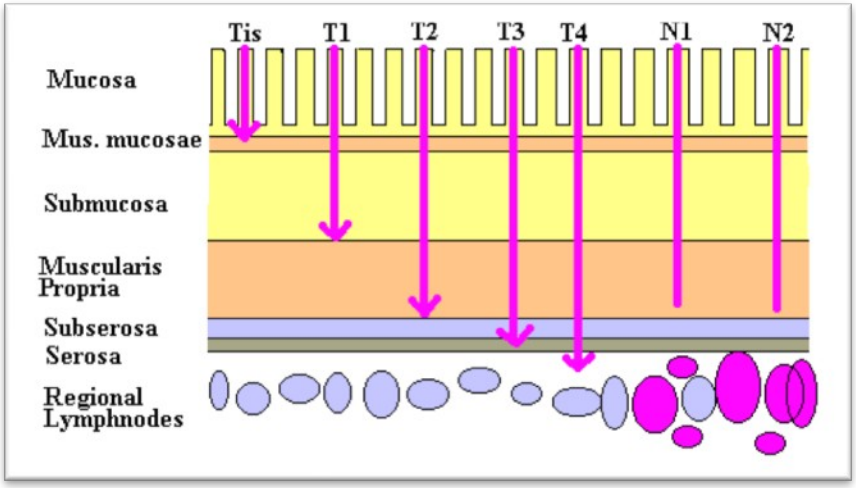
The TNM Staging System

The systems described by AJCC and UICC using TNM classifications were unified into one in 1988 [41]. The latest revision (1997) has introduced some minor modifications. The TNM system compartmentalizes carcinomas according to the depth of invasion of the primary tumour, the absence or presence of regional lymph node metastases, and the absence or presence of distant metastases. The possible number of resulting categories is too large (24 or more if Tis is included) for practical usage. Various categories are therefore grouped under stages I through IV. 'cTNM' is based on evidence acquired before treatment and 'pTNM' is based on clinical staging and information obtained at surgery and pathological examination of the resected specimen.

Many additional descriptors are used in conjunction with the TNM classification. The 'R' classification refers to presence of residual

carcinoma after treatment. The ‘G’ classification reflects inclusion of histological grading. The ‘C’ factor is based on certainty of diagnosis, ‘L’ represents lymph vessel invasion, and ‘V’ reflects venous invasion. It is important to remember that a minimum of twelve lymph nodes should be examined for proper assessment of the ‘N’ category [42]. A tumour nodule measuring three cms or more in diameter in the perirectal or pericolic adipose tissue even without histological evidence of residual lymph node tissue in the nodule is classified as regional nodal metastasis.

TNM Staging System

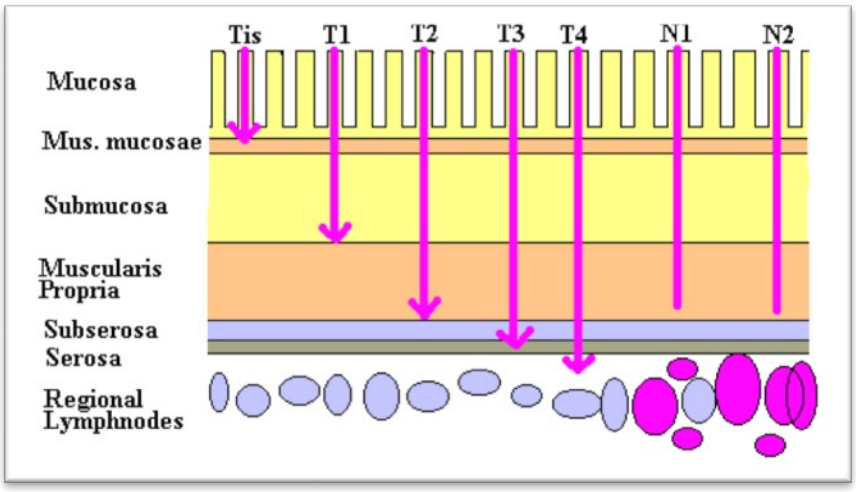


TNM Staging Classification for Colorectal Carcinomas (1997)

TX	Primary tumour can not be assessed.
T0	No primary tumour identified.
Tis	Carcinoma in situ (tumour limited to mucosa).
T1	Involvement of submucosa, but no penetration through muscularis propria.
T2	Invasion into, but not penetration through, muscularis propria.

T3	Penetration through muscularis propria into subserosa (if present), or pericolic fat, but not into peritoneal cavity or other organs.
T4	Invasion of other organs or involvement of free peritoneal cavity.

TNM Staging System



TNM Staging Classification for Colorectal Carcinomas (Contd.)

NX	Nodal metastasis can not be assessed.
N0	No nodal metastasis.
N1	1-3 pericolic / perirectal nodes involved.
N2	4 or more pericolic / perirectal nodes involved.
MX	Distant metastasis can not be assessed.
M0	No distant metastases.
M1	Distant metastases

Stage Grouping criteria for TNM Classification (1997)

Stage 0	Tis	N0	M0
Stage I	T1-2	N0	M0
Stage II	T3-4	N0	M0
Stage III	any T	N1-2	M0
Stage IV	any T	any N	M1

Lymph Nodes designated as regional for colorectal carcinomas

Caecum	Anterior caecal, posterior caecal, ileocolic, right colic
Ascending colon	Ileocolic, right colic, middle colic
Hepatic flexure	Middle colic, right colic
Transverse colon	Middle colic
Splenic flexure	Middle colic, left colic, inferior mesenteric
Descending colon	Left colic, inferior mesenteric, sigmoid
Sigmoid colon	Inferior mesenteric, superior rectal, sigmoidal, sigmoid mesenteric
Rectosigmoid	Perirectal, left colic, sigmoid mesenteric, sigmoidal, inferior mesenteric, superior rectal, middle rectal
Rectum	Perirectal, sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, internal iliac, sacral promontory, superior rectal, middle rectal, inferior rectal

The metastatic deposits in nodes distant from those surrounding the main tumour or its main artery in the specimen (e.g. external iliac or para-aortic

nodes) are counted as distant metastases and would represent M1. The specified regional lymph nodes for the colorectal cancers for different anatomical sites are given in the table above.

Other Staging Systems

Many other staging systems have been proposed trying to define a scheme which is more predictive.

The Gunderson-Sosin modification of the Astler-Coller system subclassifies B2 and C2 tumours into those with microscopic (B2m or C2m) and gross (B2m+g or C2m+g) invasion of tumour through the bowel wall [43]. The Gastrointestinal Tumour Study Group (GITSG) classification uses the number of nodes (1-4 and >4) involved to separate stages C1 and C2, respectively. The classification by Jass et al uses absence or presence of transmural penetration, pushing or infiltrative margin of primary tumour, absence or presence of conspicuous peritumoral lymphocytic infiltrate, and number of positive nodes for a mathematical stratification.

Many other local and institutional schemes exist reflecting target the current controversies.

SYMPTOMS AND SIGNS ASSOCIATED WITH COLORECTAL CANCER

- Change in bowel habits
- Weight loss
- Change in appetite
- Obstructive symptoms
- Palpable mass on digital rectal examination
- Overt rectal bleeding
- Microcytic anemia with fatigue, shortness of breath, and angina
- Vague abdominal discomfort
- Large bowel obstruction
- Pneumaturia
- Feculent vaginal discharge
- Perforation (rare)
- Weakness
- Jaundice
- Ascites

HISTOLOGY

More than 90% of cases are adenocarcinomas.

Other histological types:

- Squamous cell carcinoma
- Carcinoid
- Leiomyosarcoma
- Lymphoma

Most grading systems classify adenocarcinomas as either moderately or poorly differentiated.

PROGNOSTIC FACTORS

- Stage
- Histological grade
- Anatomic location of the tumour
- Clinical presentation
- Allelic loss of chromosome18q

Tumour penetration of the bowel wall and lymph node involvement are important prognostic factors [44]; both are associated with increased risk of local recurrence. Absolute number and proportion of involved lymph nodes are important predictors of outcome. Presence of both lymph node involvement and extension of disease beyond the bowel wall is more ominous than the presence of either alone. In patients with low rectal cancer being considered for sphincter-sparing treatment, clinical mobility, size, and morphology of the lesion are predictors of outcome. Aneuploidy

and high proliferative index (measured by adding percentage of cells in S phase to those in G2 and M phase) are associated with worse survival in colorectal cancer.

METASTASIS

Metastasis is usually by haematogenous spread, mainly to the lung and liver. Pre-treatment evaluation is valuable for proper staging and for planning treatment [45].

DIAGNOSTIC WORKUP FOR COLORECTAL CANCER

1. History
2. Physical examination, including detailed rectal examination
3. Gynaecologic examination (female patients)
4. Radiographic and endoscopic studies
    a. Barium enema or colonoscopy
    b. Proctosigmoidoscopy (if colonoscopy not done)
    c. Computed tomography or magnetic resonance imaging (pelvis, abdomen, if indicated)
    d. Intrarectal ultrasound (if indicated)
5. Routine laboratory studies
    a. Complete blood cell count

b. Blood chemistry profile, including liver and renal function studies

6. Radiogram chest
7. Carcinoembryonic antigen
8. Molecular biologic markers

Positron emission tomography (PET) scan [55, 56], magnetic resonance imaging (MRI), and ultrasound may be useful in evaluating patients with oligometastatic disease who may be appropriate candidates for resection of metastatic disease with curative intent.

CARCINOEMBRYONIC ANTIGEN

CEA is a cell-surface glycoprotein that is shed into the blood and is the best-known serological marker for monitoring colorectal cancer disease status and for detecting early recurrence and liver metastases. CEA is too insensitive and non-specific to be valuable for screening of colorectal cancer. Elevation of serum CEA levels, however, does correlate with a number of parameters. Higher CEA levels are associated with histological grade 1 or 2 tumours, more advanced stages of the disease, and the presence of visceral metastases. Although serum CEA concentration is an independent prognostic factor, its putative value lies in serial monitoring after surgical resection.

New markers, such as CA 19-9, may be of value in monitoring recurrences

and complement CEA. Monoclonal antibodies may also be useful in immuno-histo-chemical staining of tissues. The presence of an abnormal number of chromosomes in the tumour cells (aneuploidy) confers a worse prognosis than is observed in patients with diploid tumours. Light microscopic features and stage, however, remain the most reliable prognostic measures. Early reports suggest that tumour DNA and circulating tumour cells may also have utility, both as initial diagnostic tools and for early diagnosis of recurrent disease.

STAGING INVESTIGATIONS

The staging of rectal cancer involves identifying the depth of tumour penetration through the rectal wall (T) and the presence or absence of diseased lymph nodes (N) and detecting distant metastases (M). The preoperative staging of rectal cancer is based on the TNM system of classification. There are various modalities employed for staging rectal cancer, including DRE, endoscopic ultrasonography [47, 48], computed tomography (CT) [49, 50], and magnetic resonance imaging (MRI) [51, 52]. Each method has its own strengths and limitations. Optimally, a combination of these methods should be used to mitigate these limitations.

Endorectal ultrasound and MRI are commonly used to assess the extent of the primary tumour. Nodal status can be determined using MRI, CT, and EUS, but may be difficult to assess radiographically.

Accuracy of Pelvic CT, MRI and EUS for T and N staging [46, 53]

'T' stage

Investigation	Accuracy (%)	Sensitivity (%)	Specificity (%)
CT	73	78	63
ERUS	87	93	78
MRI	82	86	77
MRI-Endorectal coil	84	89	79

'N' stage

Investigation	Accuracy (%)	Sensitivity (%)	Specificity (%)
CT	66	52	78
ERUS	74	71	76
MRI	74	65	80
MRI-Endorectal coil	82	82	83

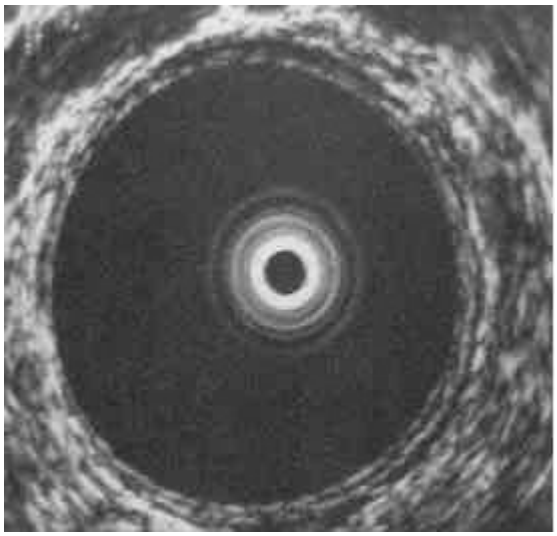
Computerized Tomography (CT)

CT has been utilized extensively and is part of the routine work-up of patients. CT appears to be much more useful in identifying enlarged pelvic lymph nodes and metastasis outside the pelvis than the extent or stage of the primary tumour. Standard CT does not permit the visualization of the layers of the rectal wall, and, therefore, its utility in the assessment of primary cancers is limited. The sensitivity of CT scan is reported as 50% to 80% accurate, with 30% to 80% specificity (65% to 75% accurate for tumour staging and 55% to 65% accurate in mesorectal lymph node

staging). The ability of CT scans for detecting distant metastasis, including pelvic and para-aortic lymph nodes, is higher than for detecting perirectal nodal involvement (75% to 87% vs. 45%). Any lymphadenopathy near the rectum seen on a CT scan should be considered abnormal.

Endorectal ultrasound (EUS)

Transrectal ultrasound demonstrating the 5 concentric layers of the normal rectal wall



EUS is able to distinguish the five layers of the rectal wall with good spatial resolution. The mucosa (innermost ring), the submucosa (middle ring), and the serosa (outermost ring) are echogenic (white rings). They are separated by 2 hypoechoic (black) rings, the muscularis mucosa (adjacent to the mucosa) and the muscularis propria (adjacent to the serosa); the rings are best seen in the 5-o'clock position in the full-size view. The rectal wall is visualized as 5 concentric bands as follows:

1) Mucosa (echogenic)
2) Muscularis mucosa (hypoechoic)

3) Submucosa (echogenic)
4) Muscularis propria (hypoechoic)
5) Serosa (echogenic)

Transrectal endoscopic ultrasound techniques have been more helpful in efforts to clinically stage rectal cancers. EUS can be 80% to 95% accurate in tumour staging and 70% to 75% accurate in mesorectal lymph node staging. The transrectal ultrasound is very good at demonstrating layers of the rectal wall especially the mucosa, muscularis mucosa, submucosa, and muscularis propria. Its use is limited to lesions <14 cm from the anus and not applicable for the upper rectum or for stenosing tumours. EUS can also identify enlarged perirectal lymph nodes but is not effective outside of the perirectum. One area where EUS can be very useful is in determining extension of disease into the anal canal, which is an area that is poorly visualized on CT but of critical importance for planning sphincter preserving surgical procedures.

Magnetic Resonance Imaging (MRI)

Recently, MRI techniques have been found to be of greater accuracy in defining the extent of rectal cancer extension and also determining the location and stage of tumour. Different approaches to MRI have been explored including the use of body coils, endorectal MRI and phased array techniques. Although MRI appears to have greater accuracy, it requires a significant learning curve but is becoming a greater part of the standard

pre-surgical work-up for rectal cancer.

Body coil MRI, which first became available in the mid-1980s, has had an accuracy of 54% to 66% for T staging, but this has improved with the use of endorectal coil MRI with reported accuracy rates of 80% to 95%. A significant advantage of both endorectal coil and surface coil MRI is that it is less operator-dependent and permits a larger field of view than EUS. It also allows assessment for proximal tumours and stenotic lesions where EUS is not an option. Another advantage of MRI is that it can detect involved lymph nodes on the basis of characteristics other than size. MRI can also be very helpful in determining the extent of lateral extension of disease, which is critical in predicting the adequacy of circumferential margins for surgical excision. Several studies using phased array MRI have reported accuracy rates of 80% to 97% in predicting lateral disease extent and have correlated the likelihood of tumour-free resection margin by visualizing tumour involvement of the mesorectal fascia.

TREATMENT

Preoperative staging is crucial for determining the approach in the treatment of rectal cancer. In the last two decades, the treatment of rectal cancer has evolved from a single treatment to multiple options based on the disease stage at diagnosis. The techniques of radical resection and reconstruction have been refined, the role and results of local excisions are

better defined, and neoadjuvant treatment has decreased the rate of local recurrence and has improved survival rates. The correct staging of rectal lesions helps to determine the appropriate surgical management and to identify those patients who would benefit from preoperative adjuvant therapy [54].

In early stage rectal carcinoma only surgery could be the treatment [61] but not for patients with stage II or III rectal cancer. 60%–80% of patients with rectal cancer have tumours that are large and biologically aggressive. Disease at this stage carries a higher risk of local and systemic recurrence after treatment. Accordingly, strategies have been developed to address these issues through locoregional resection and multimodality therapy. However, adequate surgical resection and choice of technique are the most critical treatment factors determining patient outcome.

SURGERY

The principles of surgical management of rectal cancer are:

1) removal of the primary tumour with adequate margins of normal tissue,
2) treatment of the draining lymphatics, and
3) restoration of function.

Transanal local excision

This is done for early cancers, T1 lesions, less than 3 cm in size, well differentiated tumours, within 8 cm of the anal verge, encompassing less than 30% of rectal wall circumference with negative nodes.

Abdominoperineal resection (APR)

APR has been considered the gold standard for surgical resection of distal rectal cancers and requires removal of the primary tumour along with a complete proctectomy, leading to a permanent colostomy. APR is associated with a slightly higher morbidity and mortality than LAR and a worse quality of life due to the presence of a colostomy. There is also a higher risk of positive margins with APR as the mesorectum is very thin in the distal segment of the rectum and lateral margins are restricted by the close presence of the prostate in the male and vagina in females.

Low Anterior Resection (LAR)

Sphincter preservation is a big step towards improving quality of life [60]. Availability of circular stapling devices has expanded the role of sphincter preserving surgical options in rectal cancers, and LARs are now being performed not just for cancers of the upper third of the rectum but also for middle and lower third cancers. About 2-cm distal margin of preserved

normal rectum is considered optimal for preservation of good bowel function. Patients should have good anal sphincter continence prior to considering sphincter-preserving options. Patient age, pelvic anatomy, gender, and body habitus can affect suitability for sphincter preservation. The absence of a colostomy, while offering a better quality of life with LAR, can be compromised with bowel urgency and frequency or poor sphincter control.

Total mesorectal excision (TME)

The mesorectum is defined as the lymphatic, vascular, fatty, and neural tissues that are circumferentially adherent to the rectum from the level of the sacral promontory to the levator ani muscles. Lateral spread of disease has been shown to occur not only at the level of the tumour but distally within the mesorectum as well. Heald et al have recommended that en bloc removal of the tumour within the envelope of the endopelvic fascia is necessary to obtain adequate lateral clearance of disease and reduce the likelihood of local recurrence. Total mesorectal excision, as they described, has now become the established standard for all radical rectal cancer resections and requires sharp dissection along the plane that separates the visceral from the parietal pelvic fascia with complete en bloc removal of the rectum so that all of the rectal mesentery remains within the envelope of the specimen. On pathological review, an adequate dissection should include 12 to 15 perirectal and pelvic lymph nodes. Careful nerve

sparring dissection with TME reduces the incidence of retrograde ejaculation.

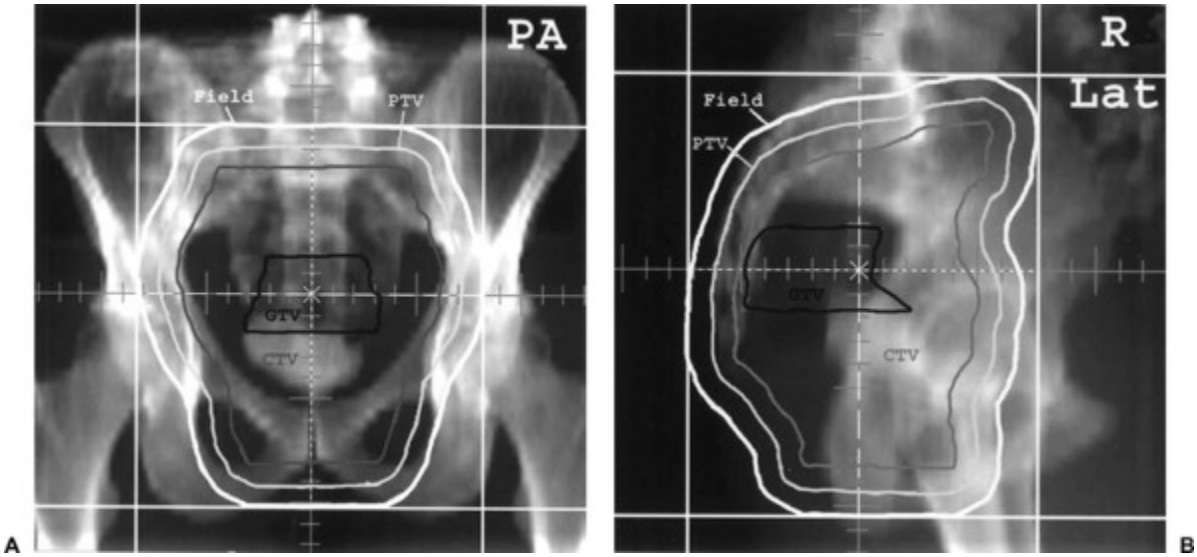
A number of European surgeons have advocated TME. They claim a low local recurrence rate but have also noted that rectal stump devascularization results in a higher rate of postoperative anastomotic site leakage. A recent report indicated that radiation after TME reduces the rate of local recurrence at 2 years from the time of surgery suggesting that radiation is still a valuable tool in reducing local recurrence even after the more extensive en bloc resection done with TME.

RADIOTHERAPY FIELDS AND TECHNIQUES

Patients are commonly treated with a three-field technique consisting of a PA and lateral fields [58, 59]. When inclusion of the anterior pelvis is indicated (e.g., treatment of the external iliac lymph nodes) an additional AP field may be advantageous. High-energy photons and appropriate beam wedging and weighting are mandatory to ensure a homogenous dose distribution within the pelvis.

Preoperative RT fields for a patient with cT3N1 carcinoma of the midrectum treated

with a three-field technique



Posteroanterior (PA) (A) and right lateral (B) fields which encompass the target volumes are devised (left lateral not shown).

PTV- planning target volume; GTV- gross tumor volume; CTV- clinical target volume

Traditional field design has been based on bony landmarks, the location of contrast-enhanced bowel / rectum and the anal verge. The superior border of the PA (and AP) field(s) generally covers the sacral promontory, while the inferior border is placed at least 3 to 4 cm distal to the rectal cancer. For upper rectal cancers, the distal border need not include the entire anal canal, but should extend to the dentate line (approximately 2 cm from the anal verge) so that all the mesorectum is encompassed. The lateral borders of the PA field should include 1.5- to 2-cm margin beyond the pelvic brim, with appropriate blocking of almost all of the femoral head. Lateral fields should cover the anterior bony margin of sacrum with 1.5- to 2-cm margin posteriorly to allow for setup error and dosimetric coverage. Anteriorly,

the field includes the internal iliac lymph nodes by placing its border on the posterior edge of pubic symphysis. Care is taken, however, when devising this border to ensure at least 3 cm coverage of the primary tumour anteriorly. In the superior-anterior portion of the field, it is usually possible to block a portion of small bowel. Similarly, the anterior genitalia in most patients should be blocked in the lateral fields.

Custom boost fields are devised that include the GTV (or tumour bed) with a 2- to 3-cm margin. A three-field technique or laterals alone will often suffice.

CHEMOTHERAPY

The treatment of rectal cancer has evolved substantially over the past two decades. In the past, rectal cancer was frequently treated with surgery alone, which resulted in high rates of local failure, with significant patient morbidity and mortality. Sentinel trials in the 1980s to early 1990s demonstrated that adjuvant chemoradiotherapy resulted in lower rates of local failure and superior survival versus resection alone [62]. This observation led to the adoption of adjuvant chemoradiotherapy as standard treatment for patients with stage II/III disease.

Mitomycin C

Mitomycin C, isolated from Streptomyces caespitosus, was introduced in 1958, and was subsequently shown to have a moderate in vitro hypoxia selective cytotoxicity. The cytotoxicity of mitomycin C is associated with

formation of monofunctional alkylation and more potently with intra- and inter-strand crosslinks of DNA, all of which require bioreductive activation. The one-electron reduction of mitomycin C results in a semiquinone, which, under hypoxic conditions, activates the aziridine ring and results in binding of the drug to DNA . Following the initial covalent attachment of mitomycin C to DNA, the drug can undergo further reductive activation to form a second alkylating site. The one-electron reduction pathway can be catalysed by any of several enzymes including NADPH, cytochrome P450 reductase and xanthine oxidase (Pan et al. 1984), in a process that can be reversed by O_2. Mitomycin C can also be reductively activated via two-electron reducing DT-diaphorase generating an O_2-insensitive hydroquinone. Despite variable results in hypoxia selective cytotoxicity observed in preclinical studies, clinical trials have reported that mitomycin C in combination with radiation shows a significant benefit in local regional control rates for patients with head and neck cancer. It is metabolized mainly in the liver by P450 system and DT-diaphorase and excreted through the hepato-biliary system.

The toxicities of mitomycin C include:

- Myelosuppression
- Nausea and vomiting
- Skin necrosis, being a vesicant drug
- Alopecia
- Photosensitivity
- Haemolytic-uremia-like syndrome

5-Flurouracil (5-FU)

5-FU is an antimetabolite that was synthesized by Dr. Charles Heidelberger in 1957. It is the most widely used drug showing wide range of activity in broad range of solid tumours. It is the backbone for various regimens used to treat advanced colorectal cancer. 5-FU enters the cells via uracil transport mechanism and is then anabolized to various cytotoxic nucleotide forms by several biochemical pathways.

5-FU exerts its cytotoxic effects through various mechanisms:

a. inhibition of thymidylate synthatase leading to depletion of deoxythymidine triphosphate, thus interfering with DNA biosynthesis and repair
b. incorporation into RNA resulting in alterations in RNA processing and/or mRNA translation
c. incorporation into DNA resulting in inhibition of DNA synthesis and function

In addition to the above mechanisms, TS inhibition may also activate programmed cell death pathways in susceptible cells leading to parental DNA fragmentation. 5-FU cytotoxicity many be mediated by activation of *Fas*-signalling pathways. It is cell cycle s-phase specific but acts in other cell cycle phases as well. 5-FU rapidly enters all tissues including spinal fluid and malignant effusions. Most of the drug is degraded in the liver. Inactive metabolites are excreted in urine, bile and breath. The elimination half-life is short - 10 to 20 minutes.

The toxicities of 5-FU are more severe in patients with dihydro-pyrimidine dehydrogenase deficiency. They include:

- mylosuppression
- mucositis
- excessive lacrimation due to dacryocystitis and lacrimal duct stenosis
- photosensitivity
- reversible cerebellar dysfunction
- somnolence
- confusion or seizure
- oesophagitis
- hand-foot syndrome
- nausea and vomiting
- black hairy tongue

It is contraindicated in patients of active ischemic heart disease or history of myocardial infarction within previous six months and in those patients who had grade III / IV mylosuppression.

NEOADJUVANT TREATMENT

The oncology community agrees on combined modality therapy but there is a great debate over the neoadjuvant versus adjuvant therapy. Proponents of neoadjuvant therapy believe that it improves sphincter preservation and thereby quality of life, allows otherwise unresectable disease to be surgically excised [63] and delivers improved outcomes of local control. Opponents contend that the surgical procedures are made more difficult after radiation, healing is impaired and overtreatment of early stage

patients occurs.

Variations in the use of RT alone or combined with chemotherapy and in surgical techniques have been investigated in attempts to improve local control rates. Numerous randomized controlled studies of both preoperative and postoperative RT alone have demonstrated no improvement in survival; at best, there has been a small decrease in the rate of local recurrence.

A number of European surgeons have advocated TME. They claim a low local recurrence rate but have also noted that rectal stump devascularization results in a higher rate of postoperative anastomotic site leakage. A recent report indicated that radiation after TME reduces the rate of local recurrence at 2 years from the time of surgery suggesting that radiation is still a valuable tool in reducing local recurrence even after the more extensive en bloc resection done with TME.

Neoadjuvant radiotherapy

Neoadjuvant radiotherapy effectively improves local control. Biologically effective dose of <30 Gy provides significant improvement in local failure and survival (at 5 years), but it does not improve overall survival or rate of distant metastasis.

Dutch colorectal cancer group (CKV095-04) compared short course RT followed by TME versus TME alone, in 1861 patients with clinically resectable disease. A total dose of 25 Gy in five fractions was delivered

over 5 days. There was a decrease in local recurrence at 2 years, which was maintained till 5 years. The overall survival rates were 64.2% and 63.5% which showed no benefit with RT followed by TME.

Swedish rectal cancer trial randomized 1168 patients with resectable rectal cancers to 25 Gy in 5 fractions preoperatively versus surgery alone. At 5 years, recurrence rates were 12% and 25% respectively. The overall survival showed benefit of 10% favouring preoperative RT.

French Lyon R96-02 trial evaluated T2 / T3 rectal cancer by comparing external RT 39 Gy in 13 fractions with same dose external RT along with 3 fractions of contact x-ray boost therapy up to 85 Gy. A total of 88 patients were randomized. A higher complete response rate was noted in the boost group compared with the no-boost group (24% versus 2% respectively). Sphincter preservation also improved in the boost arm.

Neoadjuvant chemoradiotherapy

The effect of combined preoperative chemo-radiotherapy has been demonstrated in various trials.

The EORTC 2291 trial evaluated 1011 patients with resectable T3 / T4 lesions. Radiotherapy consisted of 45 Gy over 5 weeks and chemotherapy consisted of 5-FU / leucovorin for 5 days for 2 cycles preoperatively and 4 cycles postoperatively. The 5-year local recurrence rate in the arm receiving RT alone was 17% while it was 8.5% in chemoradiotherapy arm.

Overall survival was the same in both the arms.

The German rectal cancer study group evaluated preoperative versus postoperative chemotherapy. They randomized 823 patients to receive preoperative 50 Gy RT along with infusional 5-FU during RT and 4 cycles postoperatively. Five year survival was same in both arms, but it showed local failure was higher in postoperative arm.

The French rectal cancer trial, FFCD 9203, compared preoperative RT [64] and preoperative chemoradiation [68] in 733 patients. They received preoperative RT 45 Gy over 5 weeks with or without 5-FU / LV during the first and fifth week of radiation. At 5 years, local recurrence rate was 8% in chemoradiation arm and 16% in radiation only arm. Difference in overall survival was not significant.

The New England Journal of Medicine reported a trial conducted by the North Central Cancer Treatment Group (NCCTG 794751) from 1980 to 1986 which served as the basis for the Consensus Conference recommendations. This study involved the participation of about 200 patients. Beginning four to ten weeks after curative intent surgery for stage II or III rectal cancer, patients were randomized to receive either combined modality radiation plus chemotherapy or radiation therapy alone. In both treatment regimens, radiation therapy consisted of 45 Gy to the pelvis delivered over four and one-half weeks followed by a 5.4-Gy boost to the tumour bed. In the combined modality treatment, patients received an

initial nine-week cycle of 5-FU and methyl-CCNU. This chemotherapy was followed by radiation plus concurrent 5-FU. Patients then received another nine-week cycle of 5-FU and methyl-CCNU.

With further follow-up, the results of this study show a clear advantage for the combined modality treatment in all parameters of evaluation, including reduced overall recurrences ($p=0.0016$), reduced local recurrences ($p=0.036$), reduced distant metastases ($p=0.011$), and improved survival ($p=0.026$). There is a 46% reduction in pelvic recurrence, a 37% reduction in distant tumour spread, and a 29% reduction in patient deaths. Severe acute toxicity was infrequent. Severe delayed reactions, usually bowel obstruction requiring surgical intervention, occurred in about 6.5% of all patients and were comparable in incidence whether patients received radiation therapy alone or radiation plus chemotherapy.

ADJUVANT TREATMENT

Postoperative Radiation Therapy

This allows selection of patients with high risk features who would benefit from adjuvant treatment. The disadvantage includes hypoxia of post-surgical tumour bed and increased small bowel in pelvis increasing the toxicity.

Uppasala trial compared short course preoperative radiotherapy 25.5 Gy over 5 days to conventional fractionation 60 Gy over 8 weeks postoperative radiotherapy. A total of 471 patients were randomized in this study. Preoperative treatment was well tolerated and the local recurrence rate was less in the preoperative RT, 12% versus 21%.

Intergroup 0147 trials evaluated preoperative versus postoperative therapy. It closed early due to poor accrual.

Local excision followed by adjuvant therapy was studied by Chakravarti et.al (1999) on 99 patients who underwent transanal excision – 47 received adjuvant radiation, 26 patients received concurrent 5-FU. Five-year local control and disease free survival were 72% and 66% respectively, and 90% and 74% for the adjuvant therapy group.

Postoperative chemotherapy

A subset analysis of select T3N0 patients without adverse features were noted to have no benefit from local radiotherapy. This group may be best treated with surgery and adjuvant chemotherapy.

Postoperative chemoradiotherapy

The commonly employed chemotherapy schedule in combination with

radiation is 5-FU based, with or without LV [65, 66, 67]. Two Intergroup trials (0114 and 0144) evaluated postoperative 5FU based regimens with adjuvant RT. Both had similar end points.

Intergroup 0114 examined 1695 patients with T3/T4 and node positive disease with postoperative adjuvant chemotherapy and radiation therapy. Patients were treated with 2 cycles of chemotherapy followed by concurrent chemoradiation 45 Gy, with a boost to 50 to 54 Gy, followed by 2 final cycles of chemotherapy. No difference in overall survival, disease free survival and local control was found.

Krook et al evaluated 204 patients with deeply invasive or node positive rectal cancer with postoperative radiotherapy (45 to 50 Gy) alone or in combination with 5-FU. The combined modality arm showed better improvement in local control and cancer specific death.
The Gastrointestinal Tumour Study group (GITSG) protocol GI-7175 randomized 227 patients to observation, postoperative chemotherapy, postoperative radiotherapy and combined chemotherapy & radiotherapy. Results revealed significant improvement in combined modality treatment over no adjuvant therapy for time to recurrence.

The most effective adjuvant approach, which has become standard practice in the United States, employs combined 5-FU chemotherapy and RT. This approach has significantly reduced the rates of local recurrence, distant

metastasis, and cancer-related deaths among patients with stage II and III rectal cancer. The addition to RT of 5-FU (given either by rapid injection or by continuous intravenous infusion throughout the period of radiation) apparently was crucial to the marked reduction in the local recurrence of rectal cancer.

The current standard therapy for stage II and III rectal cancer is 5-FU bolus, 500 mg/m^2/day for 5 days each month for 2 months, both before and after RT. During RT (5,040 cGy), 5-FU is given as a radiosensitizer at a dose of 225 mg/m^2/day by continuous IV infusion. The addition of a nitrosourea, levamisole, or leucovorin to the regimen did not improve the results.

Preoperative versus postoperative RT

Treatment with RT and 5-FU sensitization is becoming more and more common as a preoperative strategy to reduce the likelihood of incomplete resections and to downstage disease in patients with fixed (T4) or node-positive disease as indicated by endorectal ultrasound and biopsy.

BRACHYTHERAPY

Intraoperative interstitial and endocavitary radiation improves local control in locally advanced and recurrent rectal cancers [69]. 10 to 12.5 Gy were

given for complete resection, 12.5 to 15 Gy for microscopic residual, and 17.5 to 20 Gy for gross residual disease. The 5-year local control was 90%, 65%, 55%, and the disease specific survival at 5 years was 65%, 45%, and 15%, for these three dose levels, respectively. IORT improved local control.

Memorial Sloan Kettering Cancer Hospital treated 68 patients, over a 4-year period, for locally advanced unresectable rectal cancer with neoadjuvant 5-FU/LV followed by surgery and IORT. High dose rate IORT, consisting of 10 to 20 Gy, was delivered using Harrison-Anderson-Mick applicator. Median follow up was 17.5 months. 81% patients had local control at 2 years. For patients with recurrent disease the 2-year local control rate was 63%.

INTRAOPERATIVE ELECTRON THERAPY (IOERT)

Massachusetts General Hospital studied 73 patients with locally advanced rectal cancer who received IOERT due to tumour adherence or residual disease [70]. Patients received neoadjuvant RT with concurrent 5-FU. At 5 years, local control was associated with the extent of resection. Complete resection and IOERT yielded better results; local control and disease specific survival of 89% and 63% respectively compared with 65% and 32% in 28 patients undergoing IOERT for residual disease. The 5-year complication rate was 11%.

Predictive value of 18F-FDG PET in the management of rectal cancers

18F-FDG PET has a high predictive value in the therapeutic management of colorectal cancer. This technique could be an asset for improving patient care by reducing the effort, costs, and morbidity associated with the treatment in nonresponders. The available studies on chemotherapy response monitoring in advanced colorectal cancer and on preoperative radiotherapy and multimodality treatment response evaluation in primary rectal cancer indicate that 18F-FDG PET is a significant predictor of therapy outcome in both situations. In primary rectal cancer, 18F-FDG PET is applicable after neoadjuvant treatment in a preoperative setting (important for the preoperative selection for an individually tailored surgical approach) and correlates better with pathology than morphologic imaging modalities.

Interestingly, when 18F-FDG PET is able to predict the final outcome, it may be used to guide adjuvant chemotherapy for rectal cancer after optimal neoadjuvant and local treatments.

BACKGROUND OF THE PRESENT STUDY

At Cancer Institute, the usual protocol for locally advanced rectal cancer is neo-adjuvant chemo-radiation followed by surgery. The chemotherapy schedule used is Mitomycin-c and 5-Flurouracil concurrently with radiation. In order to analyze the effect of this multimodal approach, this study was planned.

AIM OF THE STUDY

To study the outcome of patients with locally advanced rectal cancer treated with neo-adjuvant chemotherapy and radiotherapy at the Institute from 2002 to 2006.

MATERIAL AND METHODS

224 patients with locally advanced (T2-T4/N0-N2 disease), pathologically confirmed adenocarcinoma of the rectum, without detectable distant metastasis at presentation, and who were registered at the Institute between January 2002 to December 2006, were taken up for the study. Those patients who had already undergone specific treatment for the rectal cancer were not included.

Pre-treatment Workup

The pre-treatment workup included:

- Detailed history
- Complete physical examination including detailed rectal examination
- Hematology and biochemistry
- Chest X Ray, ECG and Echo
- Colonoscopy
- Histopathological examination
- CT Scan Abdomen and pelvis
- CEA

Treatment Protocol

After taking an informed consent, patients were taken up for first cycle of chemotherapy with Mitomycin C and 5-Flurouracil from day 1 to day 5 followed by radiotherapy. At 30 Gy of RT, patients received second cycle of chemotherapy with 5-FU (x 5 days) only. Radiotherapy was continued to a total of 50 Gy. Patients were reassesed six weeks after the end of chemoradiation for surgery. In suitable patients, either an APR or LAR was done, depending upon the clinical situation. Following surgery, they received adjuvant 5-FU based chemotherapy, once in 3 weeks, to a total of 6 cycles.

Radiotherapy protocol

Radiation was given with 6-MV Xrays, with '4 fields box' technique (AP / PA / 2 Laterals), delivering 200 cGy per fraction, to a total dose 50 Gy to the whole pelvis after simulation.

Chemotherapy protocol

The firct cycle of chemotherapy included:

Inj Mitomycin C at a dose of 6 mg/m^2 IV on day 1, and

Inj 5-Flurouracil at a dose of 375 mg/m^2 IV on day 1 to day 5

In the second cycle, Inj Mitomycin C was not given.

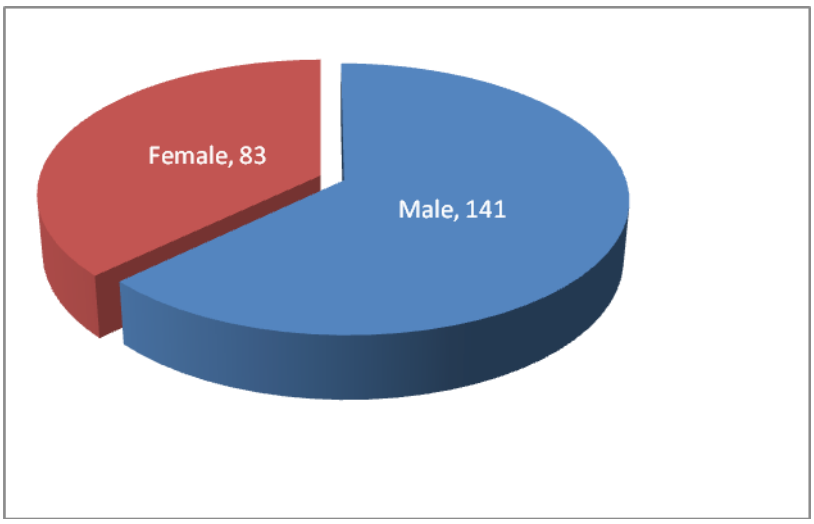
RESULTS

A total of 224 patients with locally advanced (T2-T4/N0-N2 disease), pathologically confirmed adenocarcinoma of the rectum, without detectable distant metastasis, registered at the Institute between January 2002 to December 2006, were taken up for this study.

AGE-WISE DISTRIBUTION

The age of these patients varied from 21 yrs to 90 yrs. Majority of the patients were in the 6th decade of life as shown below:

GENDER-WISE DISTRIBUTION



There were 141 (62.9%) male patients and 83 (37.1%) female patients in the study. The male:female ratio was 1.7:1.

STAGE-WISE DISTRIBUTION

The following table shows the stage-wise distribution of these patients:

Stage	Number of patients
II A	158
II B	25
III A	4
III B	32
III C	5

TREATMENT

The treatment details of the 224 patients taken up for this study are given in the following table:

Treatment	Patients	
	No	%
Neoadjuvant chemoradiation followed by reassessment for surgery	**182**	81.3
Straight surgery	42	18.7

The details of further management of the 182 patients who had completed the neoadjuvant chemoradiation are given in the following table:

Details of the patients	Patients	
	No	%
Patients who underwent the planned radical surgery	**122**	67.0
Patients who were kept on observation only as CR was	2	1.1

achieved with neoadjuvant chemoradiation		
Patients who were advised surgery but declined it	42	23.1
Patients who were not considered suitable for surgery	16	8.8

3-year DFS & OS in 122 patients who completed the planned treatment (Neoadjuvant chemoradiation followed by surgery)

Result	Patients	
	No	**%**
3-year DFS	82	67.2
3-year OS	95	77.9

Patients on observation (N=2)

Both the patients, who achieved CR with chemoradiation itself, were only on meticulous followup with no reactivation of disease for more than 3 years.

Patients who declined surgery (N=42)

11 of 42 patients who declined surgery after neoadjuvant chemoradiation (26.2%) were alive for 3 years or beyond.

DISCUSSION

Variations in the use of RT alone or in combination with chemotherapy and in surgical techniques have been investigated in attempts to improve local control rates. Numerous randomized controlled studies of both preoperative and postoperative RT alone have demonstrated no improvement in survival; at best, there has been a small decrease in the rate of local recurrence. The addition of chemotherapy along with radiotherapy gives an added advantage in sterilizing microscopic disease in regions that either cannot be resected or ought to be spared. Neoadjuvant chemoradiation has helped down-staging the disease, increased sphincter preservation surgeries and thus leads to better quality of life in a locally advanced rectal cancer patient. In addition it decreased tumour seedling at the time of surgery and thus improved overall survival. The advantages of neoadjuvant chemoradiation do not end here. There is increased radio-sensitivity due to more oxygenated cells and absence of postsurgical morbidities and possibility of converting APR to LAR.

NSABP R – 03 trial compared neoadjuvant versus adjuvant chemoradiotherapy in the treatement of locally advanced rectal cancer. The trial randomly assigned 123 patients to preoperative chemoradiotherapy and 131 patients to post operative chemoradiotherapy. The 5 - year DFS for preoperative patients was 64.7% and for postoperative patients was 53.4%. The 5 – year OS rates were 74.5% vs 65.6% respectively. The study concluded that preoperative chemoradiotherapy compared with

postoperative chemoradiotherapy significantly improved DFS and showed a trend towards improved OS (75).

At the Institute, neoadjuvant therapy has been in practice for the last 50 years in head and neck cancers. The same was later introduced in the management of breast cancers also. The pathological and local response has been significant in these malignancies. In the same way, neoadjuvant chemoration followed by radical surgery has shown very satisfactory results in the management of locally advanced rectal cancers.

CONCLUSION

Neoadjuvant chemoration followed by radical surgery has shown very satisfactory results in the management of locally advanced rectal cancers.

FUTURE DIRECTION

The evolution of the multidisciplinary approach to the management of rectal cancer has resulted in significant improvements in disease-free and overall survival rates. Significant enhancements in sphincter preservation and quality of life have also been realized. The challenge is to further improve these endpoints through the multidisciplinary approach. Molecular targeted therapies such as bevacizumab and cetuximab represent key components of evolving treatment paradigms. Novel radiation techniques such as IMRT and novel surgical techniques may also further improve the care of the rectal cancer patient.

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